Please contact applicant's representative if there are any issues to be resolved.

Respectfully submitted,

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Compositions of AMP-18 isolated from mouse and pig antrum tissue stimulate growth of confluent stomach, intestinal, and kidney epithelial cells in culture; human, monkey, dog and rat cells are also shown to respond. This mitogenic (growth stimulating) effect is inhibited by specific antisera (antibodies) to AMP-18, supporting the conclusion that AMP-18, or its products, *e.g.* peptides derived from the protein by isolation of segments of the protein or synthesis, is a growth factor. Indeed, certain synthetic peptides whose amino acid sequences represent a central region of the AMP-18 protein also have growth-factor activity. The peptides also speed wound repair in tissue culture assays, indicating a stimulatory effect on cell migration, the process which mediates restitution of stomach mucosal injury. Thus, the protein and its active peptides are motogens. Unexpectedly, peptides derived from sub-domains of the parent molecule can inhibit the mitogenic effect of bioactive synthetic peptides and of the intact, natural protein present in stomach extracts.

There are 3 activities of the gastrokine proteins and peptides of the present invention. The proteins are **motogens** because they stimulate cells to migrate. They are **mitogens** because they stimulate cell division. They function as **cytoprotective agents** because they maintain the integrity of the epithelium (as shown by the protection conferred on electrically resistant epithelial cell layers in tissue culture treated with damaging agents such as oxidants or non-steroidal anti-inflammatory drugs NSAIDs).

The invention relates a group of isolated homologous cellular growth stimulating proteins designated gastrokines, that are produced by gastric epithelial cells and include the amino acid sequence VKEK/QKKXXGKGPGGXPPPK (SEQ ID NO: 1). An isolated protein of the group has an amino acid sequence as shown in FIG. 7. The protein present in pig gastric epithelia in a processed form lacking the 20 amino acids which constitute a signal peptide sequence, has 165 amino acids and an estimated molecular weight of approximately 18kD as measured by polyacrylamide gel electophoresis. Signal peptides are cleaved after passage through endoplasmic reticulum (ER). The protein is capable of being secreted. The amino acid sequence shown in FIG. 3 was deduced from a human cDNA sequence. An embodiment of the protein is shown with an amino acid sequence as in FIG. 6, a sequence predicted from mouse RNA and DNA.

A growth stimulating (bioactive) peptide may be derived from a protein of the gastrokine group. Bioactive peptides rather than proteins are preferred for use because they are smaller, consequently the cost of synthesizing them is lower than for an entire protein.

In addition, a modified peptide may be produced by the following method:

(a) eliminating major protease sites in an unmodified peptide amino acid sequence by amino acid substitution or deletion; and/or

(b) introducing into the modified amino acid analogs of amino acids in the unmodified peptide.

An aspect of the invention is a synthetic growth stimulating peptide, having a sequence of amino acids from positions 78 to 119 as shown in FIG. 3.

Another peptide has a sequence of amino acids from position 97 to position 117 as shown in FIG. 3.

Another peptide has a sequence of amino acids from position 97 to position 121 as shown in FIG. 3.

Another peptide has a sequence of amino acids from position 104 to position 117 as shown in FIG. 3.

An embodiment of an isolated bioactive peptide has one of the following sequences: LDTMVKEQK..GKGPGGAPPKDLMY --(SEQ ID NO: 2)-- or KKLQGKGPGGPPPK --(SEQ ID NO: 3)--. An embodiment of an inhibitor of a protein of the gastrokine group has the amino acid sequence KKTCIVHKMKK --(SEQ ID NO: 4)-- or KKEVMPSIQSLDALVKEKK --(SEQ ID NO: 5)--. (see also Table 1)

The invention also relates a pharmaceutical composition including at least a growth stimulating peptide.

A pharmaceutical composition for the treatment of diseases associated with overgrowth of gastric epithelia, includes an inhibitor of a protein of the group of gastrokines or of a growth stimulating peptide derived from the gastrokine proteins.

A pharmaceutical composition for the treatment of diseases of the colon and small intestine includes at least a growth stimulating peptide of the present invention. Examples of such diseases include ulcerative colitis and Crohn's Disease.

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(b) providing environmental conditions allowing migration of the epithelial cells.

A method for cytoprotection of damaged epithelial cells in the gastrointestinal tract of mammals, includes the following steps:

(a) contacting the damaged epithelial cells with a composition including a protein of the gastrokine group or a peptide derived from the protein; and

(b) providing environmental conditions allowing repair of the epithelial cells.

The damaged cells may form an ulcer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a human genomic nucleotide sequence --(SEQ ID NO: 11)-- of a pre-gastrokine; sequence features were determined from cDNA and PCR of human genomic DNA amph-ge8.seq Length: 7995 predicted promoter: 1405; exon 1: 1436-1490; exon 2: 4292-4345; exon 3: 4434-4571; exon 4: 5668-5778; exon 5: 6709-6856; exon 6: 7525-7770; polyA site: 7751.

FIG. 2 is a human cDNA sequence --(SEQ ID NO: 12)--; the DNA clone was obtained by differential expression cloning from human gastric cDNA libraries.

FIG. 3 is a human preAMP-18 protein sequence --(SEQ ID NO: 13)-- predicted from a cDNA clone based on Powell (1987) and revised by the present inventors; N-21 is the expected N-terminus of the mature protein.

FIG. 4 is a mouse preAMP-18 sequence --(SEQ ID NO: 14)-- determined from RT-PCR of mRNA and PCR of BAC-clones of mouse genomic DNA sequences:

predicted promoter: 1874 experimental transcription start site: 1906 translation initiation site: 1945 CDS 1: 1906-1956; CDS 2: 3532-3582; CDS 3: 3673-3813; CDS 4: 4595-4705; CDS 5: 5608-5749; CDS 6: 6445-6542; polyA site: 6636.

FIG. 5 is a mouse cDNA sequence --(SEQ ID NO: 15)-- for preAMP-18.

FIG. 6 is mouse preAMP-18 amino acid sequence --(SEQ ID NO: 16)--; RT-PCR performed on RNA isolated from mouse stomach antrum: Y-21 is the predicted N-terminus of the mature protein; the spaces indicated by .. mean there are no nucleotides there to align with other sequences in FIG. 11.

FIG. 7 is a [pig genomic DNA related to the cDNA] --cDNA (SEQ ID NO: 17)-- expressing porcine AMP-18.

[FIG. 8 is the cDNA pig sequence of AMP-18. *Based on Powell (1987). **D**-21 is the N-terminus of the mature protein - confirmed by sequencing of the protein isolated from pig stomach.]

FIG. [9] --8-- is pig pre-gastrokine (pre-AMP-18) protein sequence --(SEQ ID NO: 18)-- predicted from cDNA clone based on Powell (1987) **D**-21 is the N-terminus of the mature protein - confirmed by sequencing of the protein isolated from pig stomach.

FIG. [10] --9-- is a comparison between the amino acid sequences of human --(SEQ ID NO: 13)-- versus pig --(SEQ ID NO: 18)-- pre-gastrokine.

FIG. [11] --10-- shows a computer-generated alignment comparison of human --(SEQ ID NO: 13)--, pig --(SEQ ID NO: 18)-- and mouse --(SEQ ID NO: 16)-- predicted protein sequences determined from sequencing of cDNA clones for human and pig AMP-18, and by polymerase chain reaction of mouse RNA and DNA using preAMP-18 specific oligonucleotide primers; in each case the first 20 amino acids constitute the signal peptide, cleaved after passage through the endoplasmic reticulum membrane.

FIG. [12] --11-- shows the effect of porcine gastric antrum mucosal extract, human AMP peptide 77-97, and EGF on growth of gastric epithelial cells; AGS cells were grown in DMEM containing fetal bovine serum (5%) in 60-mm dishes; different amounts of pig antrum extract, HPLC purified peptide 77-97, and/or EGF were added; four days later the cells were dispersed and counted with a hemocytometer; antrum extract and peptides each stimulated cell growth in a concentration-dependent manner; the bar graph shows that at saturating doses, peptide 77-97 (8g/ml) or EGF (50ng/ml) was mitogenic; together they were additive suggesting that the two mitogens act using different receptors and/or signaling pathways; anti-AMP antibodies inhibited the antrum extract but did not inhibit peptide 77-97.

FIG. [13] --12-- shows the structure of the human and mouse preAMP-18 genes; the number of base pairs in introns are shown above the bars; exons are indicated E1-E6 and introns I1-I5; there are minor differences in intron length.

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TABLE 1: BIOACTIVITY OF SYNTHETIC PEPTIDES BASED ON THE SEQUENCE OF GASTROKINE (AMP-18)

Name of Peptide, Sequence in Human	#AA	AMINO ACID SEQUENCE	$K_{1/2}$,µM
78-119	42	KKTCIVHKMKKEVMPSIQSLDALVKE**KKLQGKGPGGPPPK**GL (SEQ ID NO:6)--	0.3
78-88	11	KKTCIVHKMKK (SEQ ID NO:4)--	Inactive
87-105	19	KKEVMPSIQSLDALVKEKK (SEQ ID NO:5)	Inactive
104-117	14	**KKLQGKGPGGPPPK** (SEQ ID NO:3)	0.8
104-1[illegible]	18	**KKLQGKGPGGPPPK**GLMY (SEQ ID NO:7)	1.0
97-117	21	LDALVKE**KKLQGKGPGGPPPK**--(SEQ ID NO:8)--	0.3
97-117**	21	GKPLGQPGKVPKLDGKEPLAK --(SEQ ID NO:9)--	Inactive
97-121	25	LDALVKE**KKLQGKGPGGPPPK**GLMY --(SEQ ID NO:10)--	0.2
109-117	9	KGPGGPPPK--(portion of SEQ ID NO:10)--	2.5
104-109	6	KKLQGK --(portion of SEQ ID NO:10)--	7.4
110-113	4	GPGG --(portion of SEQ ID NO: 10)--	Inactive
mouse 97-119	23	LDTMVKEQK..GKGPGGAPPKDLMY --(SEQ ID NO:2)--	0.2

Table 1: Analysis of mitogenic peptides derived from the human and mouse gastrokine (AMP-18) sequence. A 14 amino acid mitogenic domain is in bold type. *Peptides are identified by their position in the amino acid sequence of the pre-gastrokine (preAMP-18). #AA; number of amino acids in a peptide. $K_{1/2}$; concentration for half-maximal growth stimulation.

Overlapping inactive peptides can inhibit the activity of the mitogenic peptides: that is, human peptides 78-88 and 87-105 block the activity of peptide 78-119, and while peptide 87-105 blocks the activity of peptide 104-117, the peptide 78-88 does not. Peptides 78-88 and 87-105 block the activity of the protein in stomach extracts.

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WE CLAIM:

1. A group of isolated homologous cellular growth stimulating proteins designated gastrokines, said proteins produced by gastric epithelial cells and comprising the amino acid sequence --(SEQ ID NO: 1)--VKEK/QKKXXGKGPGGXPPK.

2. An isolated protein from the group of claim 1, said protein further characterized as comprising an amino acid sequence as in FIG. 7, present in pig gastric epithelia in a processed form lacking the 20 amino acids which constitute a signal peptide sequence, having 165 amino acids and an estimated molecular weight of approximately 18kD as measured by polyacrylamide gel electophoresis, said protein capable of being secreted.

3. A protein from the group of claim 1, further characterized as comprising an amino acid sequence as in FIG. 3, said sequence deduced from a human cDNA.

4. A protein from the group of claim 1, further characterized as comprising an amino acid sequence as in FIG. 6, said sequence predicted from mouse RNA and DNA.

5. A growth stimulating peptide derived from a protein of claim 1.

6. A modified peptide produced by the method comprising the following steps:

(a) eliminating major protease sites in an unmodified peptide amino acid sequence by amino acid substitution or deletion in the unmodified peptide derived from a protein of claim 1; and

(b) optionally introducing amino acid analogs of amino acids in the unmodified peptide.

7. A synthetic growth stimulating peptide, having a sequence of amino acids from positions 78 to 119 as shown in FIG. 3.

8. The synthetic growth stimulating peptide of claim 7, said peptide having a sequence of amino acids from position 97 to position 117 as shown in FIG. 3.

9. The synthetic growth stimulating peptide of claim 7, said peptide having a sequence of amino acids from position 97 to position 121 as shown in FIG. 3.

10. The synthetic growth stimulating peptide of claim 7, said peptide having a sequence of amino acids from position 104 to position 117 as shown in FIG. 3.

11. An isolated bioactive peptide comprising a sequence selected from the group consisting of LDTMVKEQK..GKGPGGAPPKDLMY --(SEQ ID NO: 2)-- and KKLQGKGPGGPPPK --(SEQ ID NO: 3)--.

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12. An inhibitor of a protein of claim 1, said inhibitor selected from the group of peptides having an amino acid sequence consisting of KKTCIVHKMKK --(SEQ ID NO: 4)--, and KKEVMPSIQSLDALVKEKK --(SEQ ID NO: 5)--.

13. A composition used for the treatment of ulcers, said composition including at least a growth stimulating peptide of claim 5.

14. A pharmaceutical composition for the treatment of diseases associated with overgrowth of gastric epithelia, said compositions comprising an inhibitor of a protein of the group of claim 1 or of a growth stimulating peptide of claim 5.

15. A pharmaceutical composition for the treatment of diseases of the colon and small intestine, said diseases selected from the group consisting of ulcerative colitis and Crohn's Disease, said composition comprising at least a growth stimulating peptide of claim 5.

16. An antibody to a protein of the group of claim 1, said antibody recognizing an epitope within a peptide of the protein that has an amino acid sequence from position 78 to position 119 as in FIG. 3.

17. An isolated genomic DNA molecule with the nucleotide sequence of a human as shown in FIG. 1.

18. An isolated cDNA molecule encoding a human protein, said protein having the amino acid sequence as shown in FIG 2.

19. An isolated DNA molecule comprising the genomic sequence found in DNA derived from a mouse, said nucleotide sequence shown in FIG. 4.

20. A mouse with a targeted deletion in a nucleotide sequence in the mouse genome that when expressed without the deletion encodes a protein of the group of claim 1.

21. A method of making a protein from the group of claim 1 or a peptide derived from a protein of claim 1, said method comprising:

(a) obtaining an isolated cDNA molecule comprising a sequence encoding the protein or peptide;

(b) placing the molecule in a recombinant DNA expression vector;

(c) transecting a host cell with the recombinant DNA expression vector

(d) providing environmental conditions allowing the transfected host cell to produce a protein encoded by the cDNA molecule; and

(e) purifying the protein from the host cell.

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22. A method to stimulate growth of epithelial cells in the gastrointestinal tract of mammals, said method comprising :

(a) contacting the epithelial cells with a composition comprising a protein from the group of claim 1 or a peptide derived from a protein of claim 1, and

(b) providing environmental conditions for stimulating growth of the epithelial cells.

23. A method to inhibit cellular growth stimulating activity of a protein of the group of claim 1, said method comprising:

(a) contacting the protein with an inhibitor; and

(b) providing environmental conditions suitable for cellular growth stimulating activity of the protein.

24. The method of claim 23, wherein the inhibitor is an antibody directed toward at least one epitope of the protein, said epitope comprising an amino acid sequence from position 78 to position 119 of the deduced amino acid sequence in FIG. 3.

25. The method of claim 23, wherein the inhibitor is selected from the group of inhibitor peptides consisting of KKTCIVHKMKK --(SEQ ID NO: 4)-- and KKEVMPSIQSLDALVKEKK --(SEQ ID NO: 5)--.

26. A method of testing the effects of different levels of expression of a protein of claim 1, on mammalian gastrointestinal tract epithelia, said method comprising:

(a) obtaining a mouse in accord with claim 20;

(b) determining the effects of a lack of the protein in the mouse;

(c) administering increasing levels of the protein to the mouse; and

(d) correlating changes in the gastrointestinal tract epithelia with the levels of the protein in the epithelia.

27. A method to stimulate migration of epithelial cells after injury to the gastrointestinal tract of mammals, said method comprising:

(a) contacting the epithelial cells with a composition comprising a protein from the group of claim 1 or a peptide derived from a problem of claim 1; and

(b) providing environmental conditions allowing migration of the epithelial cells.

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28. A method for cytoprotection of damaged epithelial cells in the gastrointestinal tract of mammals, said method comprising:

(a) contacting the damaged epithelial cells with a composition comprising a protein of the group of claim 1 or a peptide derived from a protein of claim 1; and

(b) providing environmental conditions allowing repair of the epithelial cells.

29. The method of claim 28, wherein the damaged cells are an ulcer.

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1 AGCTTTATAA CCATGTGATC CCATCTTATG GTTTCAATCC ATGCACAGGA

51 GGAAAATTGT GGGCACGAAG TTTCCAAAGG GAAAATTTAT AGATTGGTAG

101 TTAATGAAAT ACAGTTTTCC TCCTTGGCAA ATTTAATTTA CTAGCTTCAC

151 TGTATAGGAA AAAGCAGGAA AAAAATTAAA ACCAACTCAC CTCCAAACCT

201 GTTTTGAGCT TTTACTTGTC TGCCCAATTG ATAGTTTCTA CTCTCTGCTT

251 TTGATGAAAA TATTTTTTAT TATTTTAATG TAACTTCTGA AAACTAAATT

301 ATCTAGAAGC AAATAAAAAG ATATTGCTTT TATAGTTCCC AGAAGGAAAA

351 AACAAACACT AGGAAAGTTC TATCTATCAG ATGGGGGAGA TGTGATGGAG

401 GCAGTGATAT TTGAGCTGAG CCTTGAACAA TGAACAGGAG TCTACCAAGC

451 GAGAGGCTAG CGGGTGGCCC TCAAGATAAA ACAACAGCAT GTACAAAGGC

501 ATGGAGACAT ACACATCTTG ACTCTTCCAG GAATGGTGGG AACGCTGGTG

551 GAGCTAGAAT GTAGGTACAT AGCATAAAGT GGCAGACGGG AAGCCTTTGG

601 AAATCTTATT ACATAGGACC CTGGATGCCA TTCCAATGAC TTTGAATTTT

651 CTGTAGGCTG CCAGCGAAAT TTCCAAGCGT GATAGAGTCA TGTCTATCTA

701 TGCACTTCAG AAAGACAACC TCAGGGTTAA TGAAGAAAAT GCATTGGAAT

751 ATAAGAAACT GGTGACCAGA GTGATCAATT GCATGACTGT TGTGAAAGTC

801 CAGGTGAGGG GAGCTGTGGG CAAGGTCAGA GTTGAGAGGC ATTTCAGAGA

851 TAAAATGACA GTAACTAAGT AGATGTCAGG CTGAGAAGAA AGGGCTGTAC

901 CAGATATATG GTGCTATCAT TAAGTGAGCT CAACATTGCA GAAAAGGGGT

951 AGGTTTGGTG GGAGTTGCTC ACAAAACATG TTTAGTCTAA GCAAAACCAT

1001 TGCCATGGGC TCAGATAAAA GTTAAGAAGT GGAAACCATT CCTACATTCC

1051 TATAGGAGCT GCTATCTGGA AGGCCTAGTA TACACGTGGC TTTTCAGCTG

1101 TGATTTTGTT TGATTTTAGG GATTATTCTT TTTCTGAATC TGAGCAATGT

FIG. 1

1151 TAGCGTGTAA AATACTCACA CCCACAGCTT TGACTGGGTG AGAAGTTATC

1201 ATAAATCATA TTGAGTTTGT TGTGATACCT TCAGCTTCAA CAAGTGATGA

1251 GTCAGGTCAA CTCCATGTGA AAGTTCCTTG CTAAGCATGC AGATATTCTG

1301 AAAGGTTTCC TGGTACACTG GCTCATGGCA CAGATAGGAG AAATTGAGGA

1351 AGGTAAGTCT TTGACCCCAC CTGATAACAC CTAGTTTGAG TCAACCTGGT

1401 TAAGTACAAA TATGAGAAGG CTTCTCATTC AGGTCCATGC TTGCCTACTC

1451 CTCTGTCCAC TGCTTTCGTG AAGACAAGAT GAAGTTCACA GTGAGTAGAT

1501 TTTTCCTTTT GAATTTACCA CCAAATGATT GGAGACTGTC AATATTCTGA

1551 GATTTAGGAG GTTTGCTTCT TATGGCCCCA TCATGGAAAG TTTGTTTTAA

1601 AAAAATTCTC TCTTCAAACA CATGGACACA GAGAGGGGAA CAACACACAC

1651 CAGGTCCTGT TGGGGGGTGG AGAGTGAGGG GAGGGAACTT AGAGGACAGG

1701 TCAATAGGGG CAGCAAACCA CCATGGCACA CATATACCTA TGTAACAAAC

1751 CTGCACGTTC TGCACATGTA TCCCTTTTTT TTAGAAGAAG AAATAATGAA

1801 AAAAAACCTT TTTTCTATTT ATATAATCAT GGCATTTATA AGCATCTCTA

1851 TAGAGAAGGA TAATTGTGCT GAGATTAGAC AGCTGTCTGA GCACCTCACA

1901 CTGACCTATT TTTAACAAAA TGACTTTCCA CATCACCTGA TTTCGGCTCC

1951 ATGCRGGGTA AGCAGTTCCT AAGCCCTAGA AAGTGCCGAT CATCCCTCAT

2001 TCTTGAATTC CTCCTTTTAT TTACCAAAAT TCCTGAGCAT GTTCAGGAAA

2051 GATGAAAAGC TTATTATCAA AATAAGTGGC TGAGATAGAC TTCTTGTCAC

2101 ATTTGTTACA GTAAAATGGG TCTCCAAGAA AGAAAGATTT GCCTTGGGCT

2151 CTAGCATGGC CATTTATTTA AGAAAGCATC TGAAACATGA AGCTACCACA

2201 GCATCTCTCC TGTGGTTCCA GACGGAAGCC TGAGAGTCTA GGAGGAGGTG

2251 GACCGAGAAA CCCTGCCAAA GTAACTAGTA GTGCCGGGTT TCTCACAACA

2301 CGATGCAAAG GGCTAGAATT CAGATGACTA TTTTCATGTT TCAACATACT

FIG. 1 Cont.

2351 ACACACTGGA AAACGTTACG GCAGACTCTA CTTTATAATG GGGCTGCAAA

2401 TGTAAAATGA CTACTAGAAC TAGGTCCTCT TAATAGCAGC AAAGTTTAAA

2451 AGGGTCAGAG GGAGCTCCAG ACACAGGTTA GATTTGATTT CTCTCCTAGT

2501 TCTGCTGTGA ACAAGAGGTA TAAGTTTGGC CAACTCACTT AACCCCTGAA

2551 GCTCAGTTAC CTTATCTGTA AAATGATTGC ATTGTACTAG GTGTTCTCTA

2601 AAATTTCTTC TACCTCTGAC TTTTTAGGAG ACTAATTTTT AACTCCTTTT

2651 TAAGCTATTG GGAGAAAAAT TTAATTTTTT TTCAAAAGTT ACCTTGAATC

2701 TCTAGAGCAG TTCTCAAAAC TATTTTGTCC CAGGCAAAGG AAATGAGACT

2751 AGGTACCCAG AATGAGGCAC CCTGCATAAA GCTCTGTGCT CTGAAAACCA

2801 ATGTCAGGGA CCCTGTGATA AATAATTAAA CCAAGTATCC TGGGACACTG

2851 CTAGTGACAT CGCCTCTGCT GATCACTCTT GCCAGCGAGA CACTCTATAC

2901 TTGCTTTCTC ATCATTGGCA TCCAAACTGC CTACTAATCC ATTGCTTTGG

2951 AAAGTTTTTT TTAATAAAAA GATTATTTCT ATTAGGAGGA AAACATCCCA

3001 TGTTAAATAG GAAAATTAAC TGAAATCATT TTCAGATGTG ATTTTTAGCA

3051 CTTATAGCCA TTTCAAACCA TGGTATTCAT TTATACTATG CTATTTATTG

3101 TAAAACTTCT TTTTTTTTCC AAGGAAAATA AGATAGTTTG CTTTATTTTA

3151 AAACAGTAAC TTTCTTATAT TGGGGCACTG ACCAAAATTC AATACTGGTA

3201 CAAATATGTT ACCTAGGGGG TCAAAATATG TGCCAGGTGA ATTTTCTGAA

3251 TTTCTCTAAA GAGAGAATTT TAAACCTTAT AAAACAATTA GAAACAAGTG

3301 AGTGAGAGGT GAGCATCAAC AACCTGTGTA ACATAAGCCA CAGTACAAAT

3351 TTAAGCTGAA TAACCAAGCC ATGTCAGTTA TCCCAAATCA TTTTTGTTAA

3401 TATTTAGGAG GATACACATA TTTTCAATAA CTTAAAAGTG AATCTTTACT

3451 CCTATCTCTT AATACTCGAA GAAGTATAAC TTTCTTCTTT TACTAGATTT

3501 AAATAATCCA AATATCTACT CAAGGTAGGA TGCTGTCATT AACTATAGCT

FIG. 1 Cont.

3551 GAGTTTATCC AAAATAGAAA AATCATGAAG ATTTATAAAG CATTTTAAAA

3601 ATAATCATTT ATAGCAAGTC CTTGAAAGCT CTAAATAAGA AAGGCAGTTC

3651 TCTACTTTCT AATAACACCT ATGGTTTATA TTACATAATA TAATTCAACA

3701 AAACAGCATT CTGACCAATG ATAATTTATA GGAAATTCAT TTGCCAAGTA

3751 TATGTTTTAT TATAAAGTTA ATATTTTGAC CAATCTTAAA AATTTTTAAA

3801 CTCTATTCTG ACATTTCCAG AAGTATTATC TTAGCAAGTC ATCTTTATGA

3851 TACCACTTAT TAAACTGAAG AGAAACAAGA TGGTACATTC TGGGTTTTAC

3901 TTTAAAAGGG ATTTGATTCA ATAATTTGAT TTATCACTAC TTGAAAATTA

3951 CATTTTCTTC CTCAGACTGG ATGGCAATGA GATGAAAGCA GCTTTCCTGG

4001 CTCTCAACTT CCCTTCTTCA TCAATTTTTC CAGCGTTTCA TAAGGCCTAC

4051 ACTAAAAATT CTAAAACTAT ATATCACATT AATATAATTA CTTATAATTA

4101 ATCAGCAATT TCACATTATC GTTAAAACCT TTATGGTTAA AAAATGCAAG

4151 GTAAGAGAAG AAAAAAACAC ATTGAACTAG AACTGAACAC ATTGGTAAAA

4201 TTAGTGAATA CTTTTCATAA GCTTGGATAG AGGAAGAAAG AAGACATCAT

4251 TTTGCCATGT AACAGGAGAC CAATGTTATT TGTGATTTCA GATTGTCTTT

4301 GCTGGACTTC TTGGAGTCTT TCTAGCTCCT GCCCTAGCTA ACTATGTAAG

4351 TCTCACCTTT TCAAGTTTGC TACCAAAATG CATTTGCAAG GAAATGTGAT

4401 ATTAAATCAC TCTCAATCTC TTATAAACTT CAGAATATCA ACGTCAATGA

4451 TGACAACAAC AATGCTGGAA GTGGGCAGCA GTCAGTGAGT GTCAACAATG

4501 AACACAATGT GGCCAATGTT GACAATAACA ACGGATGGGA CTCCTGGAAT

4551 TCCATCTGGG ATTATGGAAA TGTAGGTAGT CAACGTGCAA TTTTCACTTT

4601 ATTGTTTAAA AATACGACTT CTTTTTAACA AAAAATGTGC ATGTTAACCA

4651 TAAAGAAATT AAAAATAAAT TCTAATTACA CATAGCATAC AGTTATAAGT

FIG. 1 Cont.

4701 AAAGGTGACC ATTTTGCTCA TCCGATTTTG TTCCCTAGAG ATAACTACTG

4751 TTAATAAGTG TTGCATGATC AGTTAAAATT CAAACCAACA AACACTATGT

4801 TCAAGGGATT GTGGGTATAT ACAACAAATA TGAACATCCT TTTGCCTTGC

4851 CTGCAGATAC CCTCAATAAT GCTGAAAGAC TTATACAACA TTACTGCTTC

4901 CAAAGCTTAG ACTATCTCAC TTTGTTTTCA AAGGAGGTTT TACGACCTTC

4951 TAAAGAGATT GAAATTGACA TTTCACCTAA AACTCGGGAA ATGTAAATGA

5001 CAATATTAAT TGGTAAGAGA GGAAAGAAGA AAGAAAGAAG GAAGGAAAGA

5051 AAGAAAGAAG GAAGGAAGGA AAGAAAGAAA GAAAGAAAGA AAGAGAGAGA

5101 AAGAAAGAAA AAGAAAAAAG AGAGAAAGAG AGAAGGAAAG AAAGAGAGAA

5151 GGAAAGGAAA AGAGAAGCAA AGAAAGAGAG GAGCAAAGAA AGGAACACTT

5201 AGCACTAGTT GGGAGACCCA ACTCTGGAAT TATCAGCTAT ATATTTAACA

5251 AACGTTATAC TTTTAAATAG CAAACTCTTT ATTGTTTCAA TTTTATCTGG

5301 TCAATTGGAA AAATAATTTT TGTCTTATCT GTCTCCTTGA AATGTGAGGA

5351 TCAAAGGAGA CTAAAACATG ATAGCTTTTA AAGTCTATTT CAGTAAAACA

5401 GACTTATATA GAGGGGTTTT TATCATGCTG GAACCTGGAA ATAAAGCAAA

5451 CCAGTTAGAT GCTCAGTCTC TGCCCTCACA GAATTGCAGT CTGTCCCCAC

5501 AAATGTCAGC AATAGATATG ATTGCCAAGC AGTGCCCCAT CCAGTGCTCT

5551 TATCCCAGCT CATCACGATC TTGGAGTTCC CATTTCTCTC TGCAGGTGGA

5601 ACTGACCTCT GATAAGAAAA GCTCCTCGGA GAACACATGC CTCACTATTT

5651 GCCATCTACT TTAACAGGGC TTTGCTGCAA CCAGACTCTT TCAAAAGAAG

5701 ACATGCATTG TGCACAAAAT GAACAAGGAA GTCATGCCCT CCATTCAATC

5751 CCTTGATGCA CTGGTCAAGG AAAAGAAGGT AAAAATAAAA GGCTTTTTAT

5801 TTTTGGTGAG GGGAGAGGTT TTACATCCTT CAGTAAATAA CGAGAAGATC

5851 ACAGTCATTC CCTCTTGACT ACAGTATGTT GTAGTGTGCA GCACAAAGGG

FIG. 1 Cont.

5901 GGAAGTTATT GGTGATTGCC TGAGGGAAGG CAACTTCTGC CACATCAAAT

5951 GCTGTGGCTC ACACCTACCT CTACAACCGC TGAGCAAAGC ACTTGAAACC

6001 TTGACTGTTA GAGGAGCAAA GCTCTGGTCA CACCAATAGG AGCCTCAGTA

6051 CTTTGCCAAG GACATTTTTC TGCAAGAGTT AGTTAGGGTT ATTAGATTTA

6101 GCAAATGAAA ATAGAAGATA TCCAGTTAGG TTTGAATTTT AGGTAAGCAG

6151 CAGGTCTTTT TAGTATAATA TATCCTATGC AATATTTGGG ATATACTAAA

6201 AAAAGATCCA TTGTTATCTG AAATTCAAAT GTAACTGGGT ATTGTATATT

6251 TTGTCTGGCC ATACTAATCC AGGTGAGTGG AAAGAAGAGA TCCATAATGT

6301 TTTAAAATAT TTGCCTGAGT TCATATTCCT ATAACTGATA AATGAGTACC

6351 TTTCATTGAC AAGGTAGAGA AAATAAATAA ACTGCATTCT CAGAAGATGA

6401 TTATTACATA GTCTAATCCA AGGAATCTAT GATGACCAAA TGAGGTCCAA

6451 GTTGCAGAAT AAATTAAGCC TCAGACTTCT GTGTTTATGA GAAGCTGAGG

6501 TTTCAAACCA GGTAAATCCC TTAGGACACT TAGAAATGCT AAGATATACA

6551 GAATAAGCTA GAAATGGCTC TTCTTCATCT TGATTATGGA AAAATTTAGC

6601 TGAGCAACAC TCACTGTTGG CCTCGTATAC CCCTCAAGTC AACAAACCAC

6651 TGGGCTTGGC ATTCATTCTC TCCCATTCTT CCTTTCTACC TCTCTTTTCC

6701 ACACTCAGCT TCAGGGTAAG GGACCAGGAG GACCACCTCC CAAGGGCCTG

6751 ATGTACTCAG TCAACCCAAA CAAAGTCGAT GACCTGAGCA AGTTCGGAAA

6801 AAACATTGCA AACATGTGTC GTGGGATTCC AACATACATG GCTGAGGAGA

6851 TGCAAGGTGA GTAGCATCCC TACTGTGCAC CCCAAGTTAG TGCTGGTGGG

6901 ATTGTCAGAC TATCCTCGCG CGTGTCCATA GTGGGCACCA GTGATGCAGG

6951 GATGGTCATC AAGGCCAACA TTTGTGCAGT GCTTGCTCTG TGCCAGGTAC

7001 TGTTCTATGT GCTTTAAGTG TGTTAACTCG GTTCTTCACA GCAATCTTAT

7051 AGGTTCTATT TTAATCCTAC TTTATGGATG AGGAAACTGA GGTACAGAGA

FIG. 1 Cont.

7101 GGTCACAAAA TCCTTGCCTG GGTCAATTCC AAGCATTTTG GCTGTGGATT

7151 CTGTGCTCTT AAATATTATG GAACACTGCC TTTTAAGTGT GAATCAAGAG

7201 TAGACTCAAG TCATATTCAA AAGAATGCAT GAATGGCTAA ATGAAAGAAG

7251 AATGCTAATA GAATCTATTA ACTTTCTATA GCTCAGACAA TCACTTAATT

7301 TCTGGACATT CAAAGAACAG CTGCACACAA ACAAAGTGTC TACCTAGGGA

7351 CCTAACTTAA TGGCAATTTT CCAGATCTCT GAATTGATTG ATTTCATCAC

7401 AACAAGTAGA TAAACCTTGA CATTAGCACA TAGCTAGTTT GGAAACCCCT

7451 ACTCCCCCAA TCCCCTCCAA GAAAAGAGTC CTTAAATAGA CATTAATATA

7501 GGCTTCTTCT TTTCTCTTTA TTAGAGGCAA GCCTGTTTTT TTACTCAGGA

7551 ACGTGCTACA CGACCAGTGT ACTATGGATT GTGGACATTT CCTTCTGTGG

7601 AGACACGGTG GAGAACTAAA CAATTTTTTA AAGCCACTAT GGATTTAGTC

7651 ATCTGAATAT GCTGTGCAGA AAAAATATGG GCTCCAGTGG TTTTTACCAT

7701 GTCATTCTGA AATTTTTCTC TACTAGTTAT GTTTGATTTC TTTAAGTTTC

7751 AATAAAATCA TTTAGCATTG AATTCAGTGT ATACTCACAT TTCTTACAAT

7801 TTCTTATGAC TTGGAATGCA CAGGATCAAA AATGCAATGT GGTGGTGGCA

7851 AGTTGTTGAA GTGCATTAGA CTCAACTGCT AGCCTATATT CAAGACCTGT

7901 CTCCTGTAAA GAACCCCTTC AGGTGCTTCA GACACCACTA ACCACAACCC

7951 TGGGAATGGT TCCAATACTC TCCTACTCCT CTGTCCACTG CTTAA --(SEQ ID NO:11)--

FIG. 1 Cont.

1 CATGCTTGCC TACTCCTCTG TCCACTGCTT TCGTGAAGAC AAGATGAAGT

51 TCACAATTGT CTTTGCTGGA CTTCTTGGAG TCTTTCTAGC TCCTGCCCTA

101 GCTAACTATA ATATCAACGT CAATGATGAC AACAACAATG CTGGAAGTGG

151 GCAGCAGTCA GTGAGTGTCA ACAATGAACA CAATGTGGCC AATGTTGACA

201 ATAACAACGG ATGGGACTCC TGGAATTCCA TCTGGGATTA TGGAAATGGC

251 TTTGCTGCAA CCAGACTCTT TCAAAAGAAG ACATGCATTG TGCACAAAAT

301 GAACAAGGAA GTCATGCCCT CCATTCAATC CCTTGATGCA CTGGTCAAGG

351 AAAAGAAGCT TCAGGGTAAG GGACCAGGAG GACCACCTCC CAAGGGCCTG

401 ATGTACTCAG TCAACCCAAA CAAAGTCGAT GACCTGAGCA AGTTCGGAAA

451 AAACATTGCA AACATGTGTC GTGGGATTCC AACATACATG GCTGAGGAGA

501 TGCAAGAGGC AAGCCTGTTT TTTTACTCAG GAACGTGCTA CACGACCAGT

551 GTACTATGGA TTGTGGACAT TTCCTTCTGT GGAGACACGG TGGAGAACTA

601 AACAATTTTT TAAAGCCACT ATGGATTTAG TCATCTGAAT ATGCTGTGCA

651 GAAAAAATAT GGGCTCCAGT GGTTTTTACC ATGTCATTCT GAAATTTTTC

701 TCTACTAGTT ATGTTTGATT TCTTTAAGTT TCAATAAAAT CATTTAGCAT

751 TG --(SEQ ID NO:12)--

FIG. 2

1 MKFTIVFAGLLGVFLAPALANYNIDVNDDNNNAGSGQQSVSVNNEHNVAN 50

51 VDNNNGWDSWNSIWDYGNGFAATRLFQKKTCIVHKMKKEVMPSIQSLDAL 100

101 VKEKKLQGKGPGGPPPKGLMYSVNPNKVDDLSKFGKNIANMCRGIPTYMA 150

151 EEMQEASLFFYSGTCYTTSVLWIVDISFCGDTVEN 185 --(SEQ ID NO: 13)--

FIG. 3

1 GAATTCAAAC AGCAGGCCAT CTTTCACCAG CACTATCCGA ATCTAGCCAT

51 ACCAGCATTC TAGAAGAGAT GCAGGCAGTG AGCTAAGCAT CAGACCCCTG

101 CAGCCCTGTA AGCTCCAGAC CATGGAGAAG AGGAAGGTTG TGGGTTCAAG

151 GAGCTTTTCA GAGTGGAAAT CTGTGGATCA GTGATTTATA AAACACAGTT

201 TCCCCCTTTA TTAGATTTGA ACCACCAGCT TCAGTTGTAG AAGAGAACAG

251 GTTAAAAAAT AATAAGTGTC AGTCAGTTCT CCTTCAAAAC TATTTTAAAC

301 GTTTACTTAT TTTGCCAAGT GACAGTCTCT GCTTCCTCTC CTAGGAGAAG

351 TCTTCCCTTA TTTTAATATA ATATTTGAAA GTTTTCATTA TCTAGAGCAG

401 TGGTTCTCAT CCTGTGGGCC ATGAGCCCTT TGGGGGGGTT GAACGACCCT

451 TTCACAGGGG TCACATATCA GATATCCTGC ATCTTAGCTA TTTACATTAT

501 GATTCATAAC AGTAGCAAAA TTAGTTAGGA AGTAGGAACA AAATAACGTT

551 ATGGTTGTGG TCACCACTAT GTTAGAGGGT CCGCAGCATT CAGAGGGTTG

601 AGAACTGTTG TTCTAGAGGC AAATAAGAAG ACAGAGTTCC TTGATAGGGC

651 CCAGAGGCAG TGAAAGAAGT TTCCACGTAG AAAGTGAAGA AGGTCTGGTG

701 TCCGAAGCAG TGAGGAACTT AAAAAAAGAA AACCAAAAAC ATTGCCAACT

751 AACAGTCCAG GAGAAGAGCG GGGCATGAAA GGCTGAGTTC CCATGGGATG

801 CCTTGAATGG AATCAGAGTG TGGGAAAATT GGTGTGGCTG GAAGGCAGGT

851 GCCGGGCATC TCAGACGCTG GTAGCTGGGG AAACAGGAAA CCCCTTTAGG

901 ATCCCAAGAT GCCATTCCAA TGAGCTTGAG ATTTTTCTCA TGGACTGCCA

951 GTGAATGTTT CTACGCTCCG GAAATTAATG TTTACTTATT TTCCATATTC

1001 TAGGGGAGAA CCCTGGGAAA AATGGAGGAC ATTCATTGAA ATATCTGAGT

1051 CCTGGGATAA GGCAGGCTTG GTCCTACAAC TCTGGTAAAA GTCCATCAGG

1101 AAGTGCCTTG ACCAAGGCTG GAGTGGAGAG CTGTTGGTGA GATGTAAGGG

FIG. 4

1151 CAAGGTTTAG TTGCTAGATA TGTAGATGGC AAGATGGTGC TGCCAACAGC

1201 CCCCAGAGCT CTAACCCACT GAGAAACCCA GGAATGAATG ATGGGAGATG

1251 GCTTTGGTGC CAGCTGCTAG TGACATGGCT GGAAAGCTGC ACTGGCTTCG

1301 AGGCCAGACA ATTCCTCAAG GAAACATCTG GCCAGGGTGC AAGGGCCAGT

1351 TTCCTTCCTT GGAGTTCCTT TCACAGCTAA GAACATCATC CCCCAACCAC

1401 TGGTTTTGTT AAAAAGTTTT CAGTATGACT TGAGCATGGT CAAGAAGCAT

1451 AGAGAGGGGG AAATAAGGGT GGAAGGAGCT GGAGAAAGCT TACAATAGGA

1501 CTGGGTAAAG GGAAGGAGAA GAAACCATTC CCGCATTCCC ATAGGAGCCA

1551 GTACCAGGAA GGGCAGGTGT ACACACAGAT CTCATCTAAG GCCATGTTTG

1601 GTTTAGGGAT TACTCTTCTC CCGAATCTGA GCAGCAGCAA TACGTAAAAT

1651 ACCCACACCC ATGGCTTCCA TATTCCAGAA CTTATCACAA ACCGTGTAGA

1701 GTTTACTGAG ATACCTTCGT CAGAGGATGA GTCAGAGGCC TCCTGCCTAA

1751 GGGCCCTACT GAGCAGGCAG CTAAAGGCTT CCGGGCCTCT GCAGCTCCAC

1801 AGATACAGGA GAGGGAAGCA GATAAGCCGT GGACTCCACC TGAGCACACC

1851 TAGCTTGAGC AAAGCTGGTC AGGTACAAAT AGCAGAGGGC TGAATGTCTG

1901 TGAGCACGCC GCCTGATCCT CTGCTCCACC ACACTCCTGC CGCCATGAAG

1951 CTCACAGTAA GTCAGATCTT CTTTTCAATG CAGCACCATA CAACATTAAT

2001 AGTCAGGGGT GAGGGGGTCT GACTCTTACG GCACTGTTAC CATAGTGGAA

2051 ATATTCTCCT TTCTTTTCAT GGAATCATGG TGTTTACAAG CATGTCCATA

2101 GAGAAGAAGA ATTGCCCCGG AAGAGCCTGT CACAGGCTGA ATACTGTAGA

2151 ATTGTCTTTC ACACCATCTG TTCCAAGGTT CTACTTAAGA CGAGCAGTCT

2201 CTGGGCTCCA GAAAGAGTCT TTCTTAGCCT TGATCTCTTT CTTATTTCTG

2251 ATTTCTCCTT TCTTATCCAT GATTTCCACT TTTACCAGTT CTGGGCATGT

FIG. 4 Cont.

2301 TCCGGTCAGA CTGGAAGATC ACTGTTGTCA AAACTAGTCT TCAACACTCT

2351 TGGCTGTTAA CATGAAAACA ACGGTCCTTG GGCCCTGTGC AAGCATTTCT

2401 TGGAGAAAGT CTCTGGGGAT GAAGCTATCT CAGTTTCCCC ACTGAAGTCC

2451 TAGGATACAG AGGCTCAAAC AGAGTGCACA TATTCAATTT CAGCATACTC

2501 TATTGGCGCT GCTTTATGAA TCATATGAAT TTATGGAATT GGAAATGTAA

2551 ACTATGACCA AGAAGCGTCC ACCTCAGAAC AGGTTGGGTG GGGAACTCCA

2601 AGCACAGGCC AGAGGGCTGC GTTTCTCTTC TAGTTCTGTC TAGAGGAGTG

2651 GTTCTCGACC TTCCTAATGC TGTGACCCTT TAATACAGTT CCTCACGTTG

2701 TCGTGACTCC CAGCCATAAA ATTACTTTCA TTGCTACTGC ATAACTGTAA

2751 TTTTGCTACC ATTATGAGTT GTAATGTAAA TATCTGATAT GCAAGATACC

2801 AGATAACCTA AGAAACGGTT GTTTGACCTT TAAAGGGGTC ACAACCCACA

2851 GGTGGAGAAC TACTGGTCTA GGGTCCTTTA CAGTCCTTTA GCTGCCTCAT

2901 TTACAGGAGA TAACATCATG CTCAAAAACT CCCTCCACAT TTGGCTTTTT

2951 GGGTTGTTTT GTTTTGTTTT TCAAGACAGG GTTTCTCTGT GTAGCCCTGG

3001 CTGTCCTGGA ACTCACCTTT GTAGACCAGG CTGGCCTCGA ACTCAGAAAT

3051 CCGCCTGCTT CTGCCTCCTG AGCGCTGGGA TTAAAGGCGT GCGCCACCAT

3101 GTCTGGCTCA CATCTGGCTT TTTAAGAGAC CGATTTTAAC TTCTTGCATT

3151 GAAAATAAAT ATAGTAGAAA TGCTTAACCT ACTAAGACAA TAAAAACAGG

3201 ATTCCTTCTG CTAGGAAGAA CACGTTCCAG ACTAAGGAAA AAAACCTTTT

3251 CAGGGCTTTC ATTACACTGT GCCATGCACT AATTTTATGT TTTCTTCATC

3301 AGTTTTCAGT GTCTGAAATT CAGTGTCAAA ATTCTAAGAC TACATATGAA

FIG. 4 Cont.

3351 TATCATTACA GTAACTCAGC AATTCTATGT TACCAGTAAG TTTTTCTGTA

3401 GTTTAAAAAA AAGGTGGAAG AAGAAAGCAC AGATAGTTTA GCACATGGGT

3451 AAAATCAGTA ACTATTTCTG ATGAGCTTGG TGAAGATGCT GTAAACCATG

3501 CGACCACCAG TCCTGTTCTC TGTGCTTTCA GATGTTCGTC GTGGGTCTGC

3551 TTGGCCTCCT TGCAGCTCCT GGTTTTGCTT ACGTAAGTCT CATTTTTCTG

3601 AAGTTCATTG TCAAAACTGC ATTTACAGTG AAATGTGATC TTAAGTCACC

3651 CTCTGCTTCT TATGAACATT AGACGGTCAA CATCAATGGT AATGATGGCA

3701 ATGTAGACGG AAGTGGACAG CATTCGGTGA GCATCAATGG TGTGCACAAC

3751 GTGGCCAATA TCGACAACAA TAACGGCTGG GACTCCTGGA ATAGCCTCTG

3801 GGACTATGAA AACGTATGTA ATGGACACAC AGGGTAAAGA TATGGTGTAG

3851 CCACCACCCA TTAAAATTTC TGAGGTGAAT TCTAGCTGTT CATGAACATT

3901 AAAAGCTACC AGTAAAAGTG CCCATTCCAC TCAAAACAAT TTTACTTTTT

3951 TGCATATAAT TATTGCTAAT AAGTATTACA CAATAGGTCG AAATTCAAAG

4001 GGATCAATAG TAAGGATAAA AACTATGTAC AAAGACAAAC ACAGCATCCT

4051 TTGGTCTTCC CTGCAGAGAG TCTCCATGAT GTTAAAGGTC CAATGTTTTA

4101 TGGAGGCTGA ATGAAATACG AATGCCTCTG TGATGGAAAA GGCCCAACAT

4151 CTTATGGAGA ATGAGTGAAG TATGAATGCT ATTAGTTGTA AGAGAAGGCG

4201 ATGCAAAGCA ACACTTGGCA CCACCTGCCA ATTACTACTT TCCTATTTAA

4251 ATGTAGTTTA AAAAGCAAAG CCTGTCTTCC CTGCCTCCTG GAAACACTGC

4301 GGATGGAGGT AGACCAAGGT ATGACAGCCT TTAAAAGTTT GTCAGCAAAA

4351 CACTCCCCCA TACACACATA CACACACCCT CCTACTACAC TGGAACTGAA

FIG. 4 Cont.

4401 GCAAAGGCAG TGGGTTAGAT ATATCCACCC TCTAAGAGTT TGCAGGTCAT

4451 CTATATATGA TAGCCAGAGA CACAACTGCA GGACAGCCAG ACTCTGAGCA

4501 CTCTCCCCAG CTCCTTGTAG CTCTGTTTCA GTGGTGACTT GTGACAAGAA

4551 TCCTGGGGAA CCTGTGCCTC ACTGTTCTCT GTCTTCTTTA ATAGAGTTTC

4601 GCTGCCACGA GACTCTTCTC CAAGAAGTCA TGCATTGTGC ACAGAATGAA

4651 CAAGGATGCC ATGCCCTCCC TTCAGGACCT CGATACAATG GTCAAGGAAC

4701 AGAAGGTAAA GTCCTGCCTT CTTCTTTGGA GTGACAGGAA GTCTTACAGT

4751 CTCCAGTACA CAGTGAAGTC ACCCCCATTC CCTCTTTGGT GGAGCATGAC

4801 AGCATGTTTG TCATGATAAA TGCCACAAAC ATGTAAAACT GTTCAGTGTC

4851 TGCCTGAATG GAGGGTGGCT TCCACTGTGT CAGATGCCGT GGCCCACATC

4901 TGCCTCTGCA GGGTCCAGTA AAGCACTGGC TATCTTGAGT GTCAGAGACC

4951 CAAAGGTCTG TACACTTCAG TACAAGCCCT CCATATTTCA AGGGCACACT

5001 CCTACAGTCG TTGGGGTTAT CAGAACTAGC AAACATAGAG ACTGGATTTT

5051 CAGATGAAAA GAAATCCTTT TTAAAGTCTA AGTATGCCTT ATACAATGTT

5101 TGAGATATTC TCAATACTAA AAAAAAAAAA ATTGTTGCTT GCTTGAAAAT

5151 CAAATGTAAC CAAGTGTCCT ATATCCAGTG TCAATCATGG CTGTAGTAGA

5201 TGGGAAGAGG GAGCCCGTGG TTTTCACAGT CAGACGCCTG AGTTATTCTT

5251 CTAAGTGATA AATTGGTTCC TATAACAAGC AAGCCAGTGA ATATAAATAA

5301 GCTCTATCTC AGAAGTTATC CTGTAGTGCT ACCCTAGAAT CTAAGAGAGC

5351 AAAAGTGCTT CAAATTTCAG AATAAGTTTT GCTTTGGACT TCTGTTTTTC

5401 TAAACAACTA TAACTTCAAA CCATCTAAGC CTCGTGGGAC ACTTAGAAAT

5451 ACCAAGCCAT TCAAAGCTAG AATTGTTTCT TCACCTTACT TGAAAACAAA

FIG. 4 Cont.

5501 ATGACAACCA AAAATTGTCC CCACTGCCCT TGTACATCTT CAGATCAGTA

5551 AAGTCCTGGG CTCAGGGATC ATTCACTTTC TTTCTTTCCT TTCACACTCA

5601 ACTTCAGGGT AAAGGGCCTG GAGGAGCTCC TCCCAAGGAC TTGATGTACT

5651 CCGTCAACCC TACCAGAGTG GAGGACCTGA ATACATTCGG ACCAAAGATT

5701 GCTGGCATGT GCAGGGGCAT CCCTACCTAT GTGGCCGAGG AGATTCCAGG

5751 TGTGTACCCT GAGATGCTGT ATATCCCAAT GCAGTACTGA GAGAGCCATC

5801 AGACACTCTA AAGTGTGACC ACAGACGGAC CAATCATGTG GATTATCAGA

5851 GCAAACACTT GCTTGCTCCT TGTCAGACAG TTGTCCATGC TTCAAAAGTT

5901 CATTAAAAAA AATAGTTCAC AGGCTCCTCA CAGAAACCTT AGTAGAATCC

5951 ACAGCTTCTG CTCTTAGTCT TACTTTTTAG AAACTGAGAC CCAGAGAAAG

6001 GTCACAAAAC TTTTGTCTGG CTCAGGTTCT ATGTCTTTAA CTTTATAGAA

6051 TACCGTCTTT CTGGGTGGGT GGGCTCTAGA GTAAACTTCA AGTGAGTTCA

6101 AGGAAAGCAT GAGAAGTAGG GAAGACCAAA TGAAAGGAGA ATGCCAATGA

6151 AATCTATCGA TTCTATAGCG CCAATGCTTA ACTCCTAGGC GTTCAAAGAA

6201 TAGTATCCAC AAGGTGTCAG CCTAAGATCC TAATCTAACA GCAAGTTTTC

6251 AGATCTCTGA AGTGAAAAGA GAAAGCAAGA GAGGAACAGA GACAGAAACA

6301 GTAAGAGACA GAGAGGCAGA GACAAAGAGA CAGGGAGAAT AGAGAGGGAT

6351 TAAAATTAAT ATATAGTTTA GAAATTACGA CTCCTCACAG TCCCTGCAGA

6401 GTCCTAGGAT AGGCACTGAT TTGGACTTCT TTTCTTCTCA CTAGGACCAA

6451 ACCAGCCTTT GTACTCAAAG AAGTGCTACA CAGCTGACAT ACTCTGGATT

6501 CTGCGGATGT CCTTCTGTGG AACATCAGTG GAGACATACT AGAAGTCACA

6551 GGAAAACAAC CCGTGGGCTC TGACCATCGC AATGCTTGAT TATGAGAGTG

FIG. 4 Cont.

6601 TTCTCTGGGG GTTGTGATTA GCTTCTTTAA GGCTCAATAA ACCCACGTGG

6651 CAGCACATCC AGTTTGTAAT GACATGCCTC ATGACTTCTA TGGGAGTCCA

6701 ATGTGGCACC TGCCAGCCTG TATTCAGGAC CTCTCCGCTA TAAAGCATCC

6751 CTCCAGAGTT TTCAAATACT ACAAAGCACA GCCTGGGTTT GGGCTCAGAT

6801 AGGCCACTGC TGCCTGACTA CATTACAGAC AAACAAGTTT TAAAAGAAAG

6851 AAAAAAGAGC TCAGAGTGGC TGGAATCAGC AAGGGTGTTT TTCCTGCAAG

6901 GAGCCAGAAG TATCAATAAT CACCCAAGGA GGAGACACTG GGAATGAGAG

6951 ACTAGAACAC ACGCCTGCAG ATACGGAGAA CCTCAGCATT GCCGCTCTCT

7001 CCCATAACTG CACACCCCCT TCTGTAAACT CTGCTTCTTT CTTTCACCTG

7051 AAGATGGCCC TTGCTTTTTT TTATTATAGG ACANGATAAC TAGACCAGAA

7101 AGTCAACCTG ACTCTCTACA TTTATATGTC TTCCCAGNTC AAGAAATATT

7151 ATTTACTGGT GAATGGCACT TCTATATTCC CTTGGTTCAA TAAGTCTACA

7201 GGATCCATTC ATTGACAGGC CAAGAGTGAG ATCACATGAT ACCCAAGCAC

7251 ATGGGTCTTT CCTTGAAGGA GAAGGATCCA --(SEQ ID NO:14)--

FIG. 4 Cont.

1 ATGTTCGTCGTGGGTCTGCTTGGCCTCCTTGCAGCTCCTGGTTTTGCTTACACGGTCAAC

61 ATCAATGGTAATGATGGCAATGTAGACGGAAGTGGACAGCATTCGGTGAGCATCAATGGT

121 GTGCACAACGTGGCCAATATCGACAACAATAACGGCTGGGACTCCTGGAATAGCCTCTGG

181 GACTATGAAAACAGTTTCGCTGCCACGAGACTCTTCTCCAAGAAGTCATGCATTGTGCAC

241 AGAATGAACAAGGATGCCATGCCCTCCCTTCAGGACCTCGATACAATGGTCAAGGAACAG

301 AAGGGTAAAGGGCCTGGAGGAGCTCCTCCCAAGGACTTGATGTACTCCGTCAACCCTACC

361 AGAGTGGAGGACCTGAATACATTCGGACCAAAGATTGCTGGCATGTGCAGGGGCATCCCT

441 ACCTATGTGGCCGAGGAGATTCCAGGACCAAACCAGCCTTTGTACTCAAAGAAGTGCTAC

501 ACAGCTGACATACTCTGGATTCTGCGGATGTCCTTTTGTGGAACATCAGTGGAGACATAC

561 TAG --(SEQ ID NO: 15)--

FIG. 5

1 MKLTMFVVGL LGLLAAPGFA YTVNINGNDG NVDGSGQQSV SINGVHNVAN

51 IDNNNGWDSW NSLWDYENSF AATRLFSKKS CIVHRMNKDA MPSLQDLDTM

101 VKEQKGKGPG GAPPKDLMYS VNPTRVEDLN TFGPKIAGMC RGIPTYVAEE

151 IPGPNQPLYS KKCYTADILW ILRMSFCGTS VETY --(SEQ ID NO: 16)--

FIG. 6

1 atgcctgact tctcacttca ttgcattggt gaagccaaga tgaagttcac

51 aattgccttt gctggacttc ttggtgtctt cctgactcct gcccttgctg

101 actatagtat cagtgtcaac gacgacggca acagtggtgg aagtgggcag

151 cagtcagtga gtgtcaacaa tgaacacaac gtggccaacg ttgacaataa

201 caatggatgg aactcctgga atgccctctg ggactataga actggctttg

251 ctgtaaccag actcttcgag aagaagtcat gcattgtgca caaaatgaag

301 aaggaagcca tgccctccct tcaagccctt gatgcgctgg tcaaggaaaa

351 gaagcttcag ggtaagggcc caggggggacc acctcccaag agcctgaggt

401 actcagtcaa ccccaacaga gtcgacaacc tggacaagtt tggaaaatcc

451 atcgttgcca tgtgcaaggg gattccaaca tacatggctg aagagattca

501 aggagcaaac ctgatttcgt actcagaaaa gtgcatcagt gccaatatac

551 tctggattct taacatttcc ttctgtggag gaatagcgga gaactaa --(SEQ ID NO:17)--

FIG. 7

1 MKFTIAFAGL LGVFLTPALA DYSISVNDDG NSGGSGQQSV SVNNEHNVAN

51 VDNNNGWNSW NALWDYRTGF AVTRLFEKKS CIVHKMKKEA MPSLQALDAL

101 VKEKKLQGKG PGGPPPKSLR YSVNPNRVDN LDKFGKSIVA MCKGIPTYMA

151 EEIQGANLIS YSEKCISANI LWILNISFCG GIAEN --(SEQ ID NO:18)--

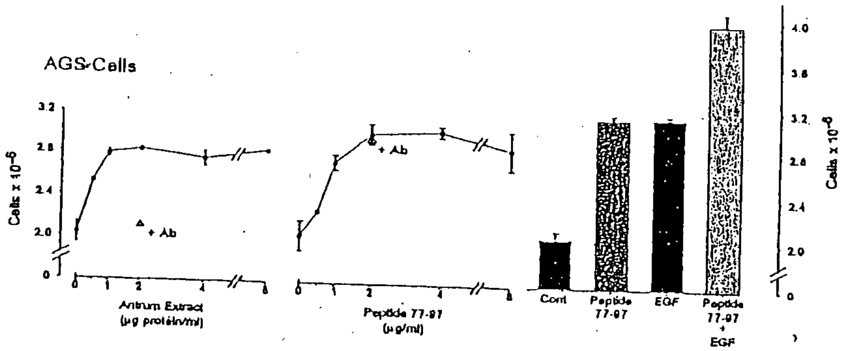
FIG. [9] 8

Human 1	MKFTIVFAGLLGVFLAPALANYNIDVNDDNNNAGSGQQSVSVNNEHNVAN	50	
Pig 1	MKFTIAFAGLLGVFLTPALADYSISVNDDGNSGGSGQQSVSVNNEHNVAN	50	
51	VDNNNGWDSWNSIWDYGNGFAATRLFQKKTCIVHKMKKEVMPSIQSLDAL	100	
51	VDNNNGWNSWNALWSYRTGFAVTRLFRKKSCIVHKMKKEAMPSLQALDAL	100	
101	VKEKKLQGKGPGGPPPKGLMYSVNPNKVDDLSKFGKNIANMCRGIPTYMA	150	
101	VKEKKLQGKGPGGPPPKSLRYSVNPNRVDNLDKFGKSIVAMCKGIPTYMA	150	
151	EEMQEASLFFYSGTCYTTSVLWIVDISFCGDTVEN	185	--(SEQ ID NO:13)--
151	EEIQGANLISYSEKCISANILWILNISFCGGIAEN	185	--(SEQ ID NO:18)--

FIG. [10] --9--

	1				50	
Human	MKFTIVF.AG	LLGVFLAPAL	ANYNIDVN.D	DNNNAGSGQQ	SVSVNNEHNV	
Pig	MKFTIAF.AG	LLGVFLTPAL	ADYSISVN.D	DGNSGGSGQQ	SVSVNNEHNV	
Mouse	MKLTM.FVVG	LLGLLAAPGF	A.YTVNINGN	DGNVDGSGQQ	SVSINGVHNV	
	51				100	
Human	ANVDNNNGWD	SWNSIWDYGN	GFAATRLFQK	KTCIVHKMNK	EVMPSIQSLD	
Pig	ANVDNNNGWN	SWNALWDYRT	GFAVTRLFEK	KSCIVHKMKK	EAMPSLQALD	
Mouse	ANIDNNNGWD	SWNSLWDYEN	SFAATRLFSK	KSCIVHRMNK	DAMPSLQDLD	
	101				150	
Human	ALVKEKKLQG	KGPGGPPPKG	LMYSVNPNKV	DDLSKFGKNI	ANMCRGIPTY	
Pig	ALVKEKKLQG	KGPGGPPPKS	LRYSVNPNRV	DNLDKFGKSI	VAMCKGIPTY	
Mouse	TMVKEQK..G	KGPGGAPPKD	LMYSVNPTRV	EDLNTFGPKI	AGMCRGIPTY	
	151			188		
Human	MAEEMQEASL	FFYSGTCYTT	SVLWIVDISF	CGDTVEN	--(SEQ ID NO:13)--	
Pig	MAEEIQGANL	ISYSEKCISA	NILWILNISF	CGGIAEN	--(SEQ ID NO:18)--	
Mouse	VAEEIPGPNQ	PLYSKKCYTA	DILWILRMSF	CGTSVETY	--(SEQ ID NO:16)--	

FIG. [1D] --10--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+ Ab
Antrum Extract
(µg protein/ml)
Peptide 77-97
(µg/ml)
Contr
Peptide 77-97
EGF
Peptide 77-97 + EGF
Cells x 10⁻⁵

FIG. [12] --11--

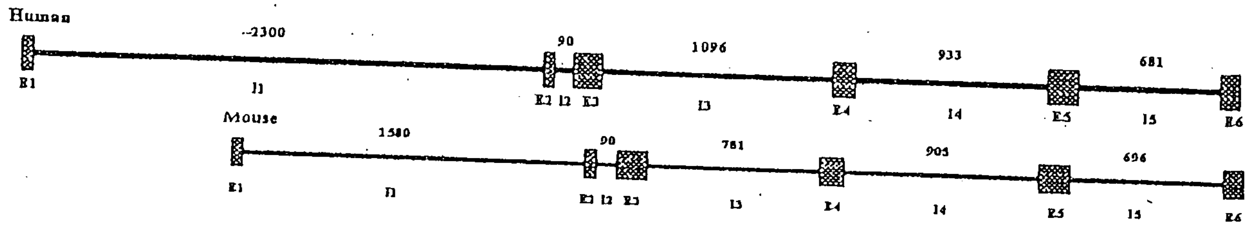

FIG. [13]--12--

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